SWISS CAPS

Docket No. 5088

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the patent application of Maier et al.
Serial No. **09/926,821**
Filing date: December 26, 2001
Title: A solid formulation of Glucosamine Sulphate
Group Art Unit **1623** -- Examiner **Krishnan**

Commissioner for Patents
Washington, D.C. 20231

DECLARATION OF Andrea Wiesmann (37 C.F.R. 1.132)

I, Andrea Wiesmann, declare that:

1. I am a Dipl. Lm. Ing. ETH. I am an employee of Swiss Caps AG since 01. January 2003.

2. The '821 application is related to a technical improvement in the formulation of the well-known active ingredient glucosamine sulphate. The '821 application teaches, for the first time, to provide an effervescent preparation comprising glucosamine sulphate as active ingredient. This preparation combines the advantages of storage-stability, usefulness as oral preparation with the possibility of providing such a high amount of glucosamine sulphate that in one single preparation a once-a-day dose can be administered.

3. In the document by Demopoulos (EP-A-0 444 000) a formulation of glucosamine sulphate is described wherein the glucosamine sulphate is mixed homogenously with ascorbic acid and calcium carbonate. According to the passage on column 7, l. 48-51 of Demopoulos, said mixture may be

used in dosage forms such as a capsule, tablet, or a suspension, or the like. The only example in Demopoulos is related to a hard gelatine capsule preparation (cf. cl. 8, l. 28-31).

4. Nowhere in Demopoulos is an effervescent preparation mentioned. A skilled man would also not have received any motivation from Demopoulos to formulate glucosamine sulphate in an effervescent preparation.

5. An effervescent formulation is characterized in that it comprises an acid component as well as a carbonate or hydrogen carbonate, which in the presence of water is capable of reacting quickly with said acid component under generation of carbon dioxide. In order to obtain the required quick reaction of the acid and the carbonate/hydrogen carbonate in the presence of water, these components have to fulfill several prerequisites. For example, the acid component has to be sufficiently acidic. Weak acids do not possess the required reactivity for quickly generating carbon dioxide, if at all, from carbonates or hydrogen carbonates.

   Another important prerequisite is that both the acid component and the carbonate/hydrogen carbonate have to be sufficiently soluble in water. It is well-known that a chemical reaction among solid reactants only proceeds very slowly, if at all. However, in an effervescent formulation the above reaction between the acid and the carbonate/hydrogen carbonate component has to proceed very quickly in order to achieve complete dissolution of the preparation in water within a very short time. A patient would not tolerate reaction times of substantially more than one minute, since he otherwise would have to wait too long before he could take the medicine.

6. Demopoulos does not disclose such an effervescent formulation. Although formally the formulation suggested by Demopoulos comprises an acidic component (ascorbic acid) as well as a carbonate (calcium carbonate), these components are not suitable of reacting quickly in the presence of water under generation of carbon dioxide:

Calcium carbonate has a very low solubility in water. Under conditions which would be acceptable for an effervescent formulation, it is not possible to quickly generate carbon dioxide from calcium carbonate. For example, while it would be possible to generate carbon dioxide from calcium carbonate with a very strong acid such as concentrated hydrochloric acid, for obvious reasons the presence of hydrochloric acid in a pharmaceutical dosage form cannot be tolerated.

Ascorbic acid, the only acid component suggested by Demopoulos, is not sufficiently acidic in order to be capable of reacting with calcium carbonate in solid form.

For these reasons, which are well-known to the skilled man, has there been no suggestion in the art to use a combination of ascorbic acid and calcium carbonate for an effervescent formulation. It simply does not function as an effervescent formulation.

Moreover, in the only example of Demopoulos a weight ratio of ascorbic acid to calcium carbonate of 1: 1.2 is used. This ratio does not make sense at all for an effervescent preparation. In effervescent preparations, an excess of acid in comparison to the carbonate/hydrogen carbonate is used in order to obtain complete conversion of the latter component, for example a more than 3-fold excess of the acid component. Demopoulos does not consider this fact at all. He only considers the ratios of glucosamine sulphate to calcium carbonate, on the one hand, and to ascorbic acid, on the other hand, for obvious reasons:

Demopoulos uses the components ascorbic acid and calcium carbonate for completely different purposes. Demopoulos believes that ascorbic acid acts as an antioxidant, thus preventing the oxidation of the oxidation-sensitive glucosamine sulphate. Moreover, Demopoulos believes that calcium carbonate acts as a desiccant, thus protecting the hygroscopic glucosamine sulphate (cf. e.g. cl. 3, l. 9-15). Demopoulos teaches that by

the combined use of the antioxidant ascorbic acid and of the desiccant calcium carbonate the storage-stability of the formulation can be increased. In other words, Demopoulos teaches the separate effects of ascorbic acids and calcium carbonate on glucosamine sulphate. He does not suggest at all the generation of carbon dioxide from those components, and therefore he need not consider the ratio of ascorbic acid to calcium carbonate.

7. As further evidence for the above, I have prepared the composition of example 1 of Demopoulos in a small scale.

500 mg glucosamine sulphate, 375 mg crystalline ascorbic acid and 375 mg calcium carbonate (i.e. the same ratio of about 1: 1.2 : 2 as in example 1 of Demopoulos) were mixed to an homogenous composition. Said composition was added into 200 ml water.

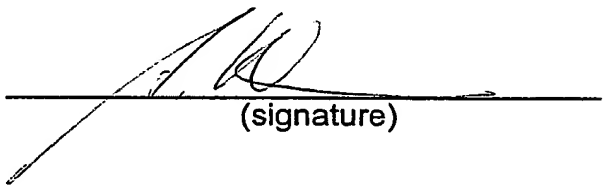
A very slight generation of carbon dioxide could be observed. However, substantially all of the calcium carbonate remained solid and sank to the bottom of the reaction flask. As expected, the reaction necessary for an effervescent formulation did not take place: Calcium carbonate has a too low solubility in water, and ascorbic acid is not sufficiently acidic in order to react with solid calcium carbonate. Moreover, the ratio of ascorbic acid to calcium carbonate applied in the reproduction of the example of Demopoulos is not suitable for promoting a substantial reaction between those components.

8. As mentioned above, Demopoulos uses the components ascorbic acid and calcium carbonate for completely different purposes. Demopoulos does not suggest at all an effervescent formulation of glucosamine sulphate, as shown above. Rather, Demopoulos is clearly limited to oral dosage forms such as tablets and capsules. The only example in Demopoulos is related to the preparation of a capsule having a fill weight of 1.0 gm (cl. 8, l. 29-30). According to my experience, capsules having a fill weight of 1,0 g are at the upper size limit for swallowable capsules. Said capsule has an amount of around 400 mg glucosamine sulphate. This is accordance with the

preferred range for glucosamine sulphate indicated by Demopoulos (cl. 6, l. 40-42). Although Demopoulos suggests to use up to 1500 mg glucosamine sulphate in a single oral dosage form, in my opinion it is not possible to administer such a high amount of glucosamine sulphate in a tablet or a capsule which should be swallowable. Tablets or capsules having such a high amount of glucosamine sulphate would be simply too large.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that the making of willful false statements or the like is punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patents issued thereon.

September 14, 2004



(signature)